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# Does treatment with *n*-3 polyunsaturated fatty acids prevent atrial fibrillation after open heart surgery?

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**Aims** To examine the effect of *n*-3 polyunsaturated fatty acid (PUFA) treatment on the incidence of post-operative atrial fibrillation (POAF).

**Methods and results** A prospective, randomized, double-blinded, placebo-controlled trial was conducted in patients admitted for coronary artery bypass grafting and/or valvular repair surgery. The patients received either *n*-3 PUFA capsules, containing a daily dose of 1240 mg eicosapentaenoic acid and 1000 mg docosahexaenoic acid, or olive oil capsules for 5–7 days prior to surgery and post-operatively until hospital discharge. The endpoint was POAF, defined as an episode detected by continuous electrocardiographic monitoring, lasting >5 min. A total of 170 patients were enrolled in the study, and 168 patients underwent surgery. Their median age was 67 (range 43–82) years, and 79.2% were males. There was no difference in baseline characteristics between the *n*-3 PUFA group ($n = 83$) and the placebo group ($n = 85$), and the incidence of POAF was 54.2 and 54.1% ($P = 0.99$), respectively. Factors associated with POAF included advanced age, peak post-operative C-reactive protein level, valvular surgery, lower body mass index, and non-smoking, but *n*-3 PUFA concentration in plasma lipids was not associated with POAF.

**Conclusion** There is no evidence for a beneficial effect of treatment with *n*-3 PUFA on the occurrence of POAF in patients undergoing open heart surgery.

**Keywords** Atrial fibrillation • Post-operative • Open heart surgery • *n*-3 Polyunsaturated fatty acids • Randomized controlled trial



## Introduction

Atrial fibrillation (AF) is the most frequently encountered arrhythmia following cardiac surgery although its incidence varies widely in reported studies, commonly ranging from 20 to 70%.[1–3] The risk of post-operative AF (POAF) increases with advancing age and the complexity of the surgical procedure.[2,4,5] Although POAF is usually a well-tolerated problem, it does, in many cases, require specific therapy, add to the length of hospital stay, increase health care costs, and may even be associated with increased mortality.[5–7]

The pathophysiology of POAF is complex and its aetiology multifactorial. Recent studies have implicated inflammation as a potential contributing factor in the development of POAF, and elevated levels of C-reactive protein and pro-inflammatory cytokines have been associated with its occurrence.[8–10]

*n*-3 Polyunsaturated fatty acids (*n*-3 PUFA) have emerged as an interesting therapeutic option for POAF, due to their proposed anti-inflammatory properties and anti-arrhythmic action.[11,12] However, there is paucity of data supporting the effectiveness of this treatment. One prospective, randomized study in patients

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undergoing coronary artery bypass grafting (CABG) surgery has demonstrated that pre- and post-operative oral administration of *n*-3 PUFA significantly reduced the incidence of POAF.[13] However, the study was neither double-blinded nor placebo-controlled, and cardiac rhythm monitoring was not performed continuously in all patients. Furthermore, no measurements of *n*-3 PUFA levels in the blood, reflecting the efficacy of the *n*-3 PUFA supplementation, were performed. Another study in CABG patients compared intravenous fish oil administration with soy oil administration for a limited time peri-operatively. In this study, the rate of POAF was decreased by half by fish oil compared with soy oil.[14] Given the requirement for additional clinical resources and increasing costs of care associated with POAF, a preventive approach using *n*-3 PUFA therapy clearly merits further evaluation.

Therefore, a study to investigate the effect of *n*-3 PUFA supplementation on the incidence of POAF following open heart surgery was undertaken.

# Methods

## Study design

The study was a prospective, randomized, double-blinded, placebo-controlled clinical trial for which patients were recruited between August 2007 and May 2009 at the Landspitali University Hospital in Reykjavik, Iceland. All consecutive patients scheduled for elective or urgent open heart surgery during the study period were evaluated for participation. Patients $<40$ years of age, those with a history of any form of supraventricular arrhythmias or taking the anti-arrhythmic medications amiodarone and/or sotalol, and patients undergoing an emergent operation were excluded. Once a decision to perform open heart surgery had been made and a scheduled date of the operation was available, the aims and protocol of the study were explained to eligible patients. Those who consented to participation were asked to discontinue intake of cod liver oil and *n*-3 PUFA capsules if they were taking such supplements but were otherwise advised to remain on their usual diet. The patients were then randomly assigned to one of the two study groups. The placebo group received 2 g of olive oil (Lysi Inc., Reykjavík, Iceland) daily, administered in two soft capsules twice per day. The treatment group received *n*-3 PUFA in two soft capsules twice daily, providing a total of 1240 mg of eicosapentaenoic acid (EPA) and 1000 mg of docosahexaenoic acid (DHA) as ethyl esters. The *n*-3 PUFA capsules are commercially available in Iceland (Omega Forte, Lysi Inc, Reykjavík, Iceland).

Randomization was stratified on the basis of age above and below 65 years and the type of surgical procedure, i.e. CABG only vs. surgery involving valve replacement or repair. The *n*-3 PUFA and placebo capsules were supplied free of charge by Lysi Inc., but otherwise there was no initiative or sponsorship by the pharmaceutical industry. The study was approved by the Bioethics Committee of Landspitali University Hospital and the Icelandic Data Protection Authority.

## Treatment protocol and study endpoints

The study drug treatment was initiated 5–7 days before the scheduled date of surgery. The patients received the last pre-operative dose in the evening prior to surgery and the first post-operative dose as soon as they could take medication by mouth. Following the operative procedure, the patients were admitted to the intensive care unit and were subsequently transferred to the thoracic surgery ward when their condition was stable. The treatment was continued until the day of discharge from the hospital or for a maximum duration of 2 weeks following the surgery in patients who experienced a prolonged hospital stay. Post-operatively, all patients underwent continuous electrocardiographic monitoring while hospitalized and the study endpoint, POAF, was defined as an episode lasting $>5$ min. Upon discharge from the hospital or 2 weeks after the surgery, the patients discontinued the study medication and exited the study.

## Data collection

Prior to surgery, all participants answered a questionnaire on their consumption of fish or cod liver oil, *n*-3 PUFA intake, smoking habits, alcohol consumption, height, body weight, and medication use. Since *n*-3 PUFA may prolong bleeding time, information on possible side effects during the study was meticulously recorded, including operative and post-operative blood loss, major bleeding, and number of blood transfusions administered. The need for re-operations in the early post-operative period, death, and cerebrovascular accidents (CVAs) were also recorded. At the end of the study, each patient answered a questionnaire regarding their participation, including self-reported side effects of the study medication and whether they thought they were assigned to the active treatment group or not.

## Blood sampling and analysis

Venous blood samples for fatty acid analysis were obtained from the patients three times during the study: immediately before the investigative treatment was initiated, on the day of surgery, and on the third post-operative day. Plasma was separated from whole blood by immediate centrifugation at 3000 rounds per minute for 10 min, and the samples were frozen at $-76^{\circ}$C and stored until the analysis of the fatty acids content in the phospholipid fraction was performed. Plasma levels of C-reactive protein were measured by an enzymatic sandwich immunoassay (Vitros 5.1 FS Chemistry System, Ortho-Clinical Diagnostics, Raritan, NJ, USA) prior to surgery and daily following surgery until the levels had peaked.

Total lipids were extracted from plasma with chloroform:methanol (2:1, v/v), using the method of Folch *et al.*[15] The antioxidant butylated hydroxytoluene (5 mg/100 mL) was added to the extraction medium. The phospholipids were separated by thin-layer chromatography (Adsorbosil H, Alltech, Deerfield, IL, USA) employing the solvent system petroleum ether–diethyl ether–acetic acid (80:20:1, v/v/v). The phospholipid fatty acids were methylated by treatment with 14% boron trifluoride-methanol (Sigma Chemical Co., St Louis, MO, USA) for 45 min at 110°C. Quantitative analysis of fatty acid methyl esters was done by gas chromatography using an HP Series II 5890 A Gas Chromatograph (Hewlett Packard Co., Palo Alto, CA, USA) equipped with a flame ionization detector and a Chrompack CP-WAX 52CB capillary column (25 m $\times$ 0.32 mm i.d. $\times$ 0.2 μm film thickness). The oven was programmed to provide an initial temperature of 90°C for

2 min, then a rising temperature by 30°C per minute to 165°C, followed by 3°C per minute to 225°C, after which the temperature was held isothermal for 6 min. The injector and detector temperatures were maintained at 235 and 250°C, respectively. Hydrogen was used as the carrier gas. The fatty acid methyl esters were identified and calibrated against commercial standards (Sigma Chemical Co.; Nu-Check Prep, Elysian, MN, USA). The software HP 3365 Chemstation, Version A.02.12 (Hewlett Packard Co.), was used for instrumental control and data acquisition and processing.

## Statistical considerations

A treatment effect similar to the effect of anti-arrhythmic medications used for the prevention of POAF was considered clinically significant. As the incidence of POAF in Iceland was unknown, we used an estimated incidence of 40% for sample size calculations on the basis of reports in the literature,[1–3] proposing a reduction to 20% by active treatment. Sample size calculations demonstrated that 80 subjects in each group would give >80% power to detect such a difference at a significance level of 0.05 (Stplan 4.1, Department of Biomathematics, M.D. Anderson Cancer Centre, The University of Texas, Houston, TX, USA).

Statistical analysis was performed on an intention-to-treat basis. We used Wilcoxon–Mann–Whitney and $\chi^2$ or Fisher's exact test to compare the groups. A stepwise multivariable logistic regression was used to examine factors associated with POAF. Data are presented as median (range) or percentages unless otherwise noted. All analyses were carried out using SPSS software (version 11.5).

# Results

Of the total of 170 patients enrolled in the study, 84 patients were randomized to the *n*-3 PUFA group and 86 to the placebo group. Two patients, one from each group, had their surgery cancelled after randomization leaving 168 patients for further analysis. The baseline and surgical characteristics of patients in the two groups were similar apart from the duration of extracorporeal circulation (ECC) (*Table 1*). The ECC time was longer in the placebo group with a median of 100.5 (range 0–261) min compared with 83 (0–254) min in the *n*-3 PUFA group ($P = 0.047$). The duration of pre-operative treatment with the study medication varied from 2 to 28 days. A total of 12 patients took the medication for <5 days, of whom three patients in the *n*-3 PUFA group discontinued the medication because of adverse effects, and additional two patients in the *n*-3 PUFA group and seven in the placebo group underwent surgery earlier than was originally planned. Sixteen patients took the medication for >10 days due to a delay of the operation, nine of whom were assigned to the placebo group.

No difference in the incidence of POAF was observed between the *n*-3 PUFA and placebo groups (54.2 vs. 54.1%, respectively; $P = 0.99$) as shown in *Figure 1*, nor in the median time to the development of POAF, 49 (25.5–163) vs. 45 (7–291.5) h, respectively ($P = 0.42$).

The total concentration of *n*-3 PUFA in plasma phospholipids in the *n*-3 PUFA group increased from a baseline of 102.5 (49.3–237.5) to 115.4 (70.9–256.1) μg/mL on the day of surgery ($P = 0.002$), whereas in the placebo group it decreased from 102.3 (51.0–224.7) to 88.5 (47.3–193.7) μg/mL ($P < 0.001$) (*Figure 2*).

**Table 1 Baseline and operative characteristics of patients in the *n*-3 PUFA and placebo groups**

| | *n*-3 PUFA group ($n = 83$) | Placebo group ($n = 85$) |
|---|---|---|
| Age (years) | 67 (45–82) | 67(43–82) |
| BMI (kg/m$^2$) | 27.5 (17.2–38.8) | 27.3 (21.2–41.3) |
| Ejection fraction (%) | 60 (15–70) | 60 (15–77.5) |
| Length of treatment (days) | 6 (2–18) | 6 (3–28) |
| Gender (% men) | 81.9 | 76.9 |
| Smoking (%) | 21.7 | 16.5 |
| Cod liver oil intake (%) | 57.8 | 51.8 |
| *n*-3 PUFA intake (%) | 27.7 | 25.9 |
| Hypertension (%) | 61.4 | 64.7 |
| Diabetes (%) | 15.7 | 15.3 |
| Use of β-blockers (%) | 78.3 | 74.1 |
| CABG only (%) | 73.8 | 74.1 |
| Off-pump surgery (%) | 14.5 | 9.4 |
| Aortic cross-clamp time (min) | 45 (0–208) | 50.5 (0–183) |
| ECC time (min) | 83 (0–254) | 100.5 (0–261)* |

Data are presented as median (range) or percentage. PUFA, polyunsaturated fatty acids; BMI, body mass index; CABG, coronary artery bypass grafting; ECC, extracorporeal circulation.
*$P = 0.047$ compared with the *n*-3 PUFA group, Wilcoxon–Mann–Whitney test.

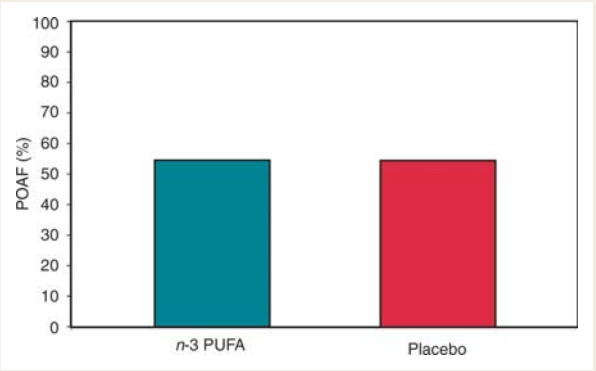


**Figure 1** Incidence (%) of post-operative atrial fibrillation (POAF) in the *n*-3 polyunsaturated fatty acid (PUFA) and placebo groups.

The total concentration of the plasma *n*-3 PUFA in the *n*-3 PUFA group decreased from 115.4 (70.9–256.1) μg/mL on the day of operation to 101.4 (45.8–187.4) μg/mL on the third post-operative day ($P < 0.001$). The concentration of plasma *n*-3 PUFA was higher on the day of surgery as well as on the third post-operative day in the *n*-3 PUFA group compared with the placebo group ($P \leq 0.001$) (*Figure 2*).

No differences in the incidence of POAF were found between the *n*-3 PUFA and placebo groups when the study cohort was divided into tertiles of *n*-3 PUFA blood levels at baseline and at the day of surgery, and of peak post-operative C-reactive protein levels (*Table 2*).

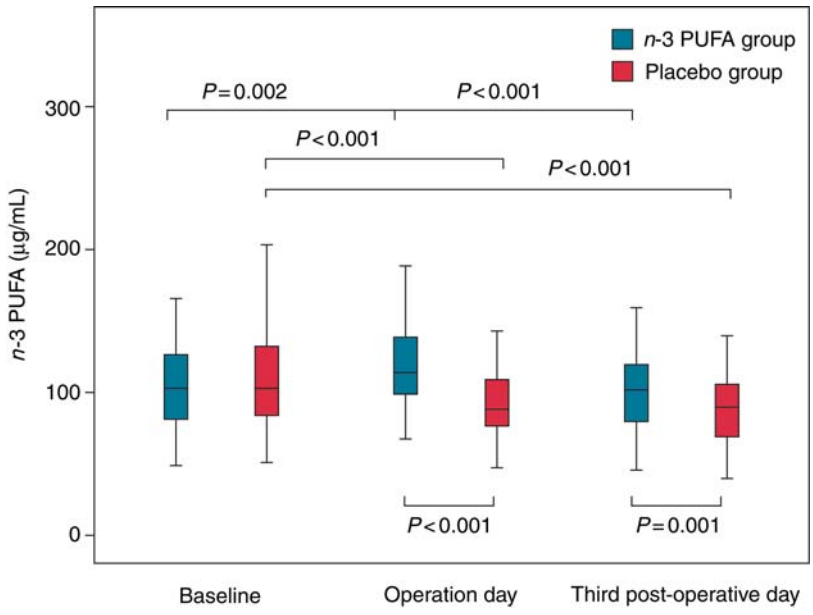


**Figure 2** Total concentration (μg/mL) of plasma *n*-3 polyunsaturated fatty acids (PUFA) of patients in the *n*-3 PUFA and placebo groups at baseline, operation day, and the third post-operative day. Data are presented as median (25th, 75th percentiles for interquartile range). The *n*-3 PUFA levels were higher in the *n*-3 PUFA group compared with the placebo group at operation day and at the third post-operative day. Within the *n*-3 PUFA group, the *n*-3 PUFA levels were lower at baseline and at third post-operative day compared with operation day. Within the placebo group, the *n*-3 PUFA levels were higher at baseline than at operation and third post-operative days. Wilcoxon–Mann–Whitney test for analysis between groups and Wilcoxon signed ranks test for analysis within groups.

**Table 2 Incidence of post-operative atrial fibrillation in the *n*-3 PUFA and placebo study groups based on tertiles of *n*-3 PUFA blood levels at baseline and at operation day, and of peak post-operative C-reactive protein levels**

| | First tertile | | Second tertile | | Third tertile | |
|---|---|---|---|---|---|---|
| | ***n*-3 PUFA ($n = 27$)** | **Placebo ($n = 28$)** | ***n*-3 PUFA ($n = 27$)** | **Placebo ($n = 28$)** | ***n*-3 PUFA ($n = 28$)** | **Placebo ($n = 29$)** |
| *n*-3 PUFA level | | | | | | |
| At baseline | 43.5 | 46.7 | 60.0 | 54.2 | 57.7 | 65.4 |
| At operation day | 35.7 | 40.0 | 48.3 | 69.2 | 63.2 | 68.8 |
| Peak post-operative C-reactive protein level | 40.7 | 50.0 | 51.9 | 53.6 | 71.4 | 58.6 |

Data are presented as percentage. POAF, post-operative atrial fibrillation; PUFA, polyunsaturated fatty acids. No significant differences were found between the two groups within each tertile, $P > 0.05$, $\chi^2$ test.

Post-operative outcomes such as blood loss, red blood cell transfusions, and frequency of re-operation or major bleeding did not differ between the two groups. Two patients in the *n*-3 PUFA group died. One of them suffered a massive myocardial infarction and heart failure on the third post-operative day and the other died from rupture of the ascending aorta on the second post-operative day. Neither of them had developed POAF. One patient in the *n*-3 PUFA group suffered a CVA compared with three in the placebo group, one of whom died after a protracted hospital course. A similar rise in peak C-reactive protein levels following the operation was observed in both groups (*Table 3*). Self-reported gastrointestinal discomfort was more common in the *n*-3 PUFA group compared with the placebo group (13.2 vs. 3.5%, respectively; $P = 0.02$), causing two patients to discontinue the intake of *n*-3 PUFA capsules prior to surgery. Overall, the *n*-3 PUFA treatment was well tolerated without serious adverse effects compared with placebo (*Tables 3* and *4*).

*Table 5* shows the baseline and operative characteristics of patients who developed POAF compared with those who did not. The age of patients who developed POAF was higher, 69 (45–82) vs. 65 (43–79) years ($P = 0.001$), and their body mass index (BMI) lower, 26.7 (17.2–38.1) vs. 28.3 (20.9–41.3) kg/m$^2$ ($P = 0.012$) compared with those who did not develop POAF. They were also less likely to have undergone isolated CABG vs.

**Table 3 Post-operative outcomes of the *n*-3 PUFA and placebo groups**

| | *n*-3 PUFA group (*n* = 83) | Placebo group (*n* = 85) |
|---|---|---|
| Estimated operative blood loss (mL) | 900 (0–4300) | 1000 (0–6200) |
| Blood volume in drains (mL) | 760 (110–3070) | 770 (175–4980) |
| Transfusion of RBC (units) | 1 (0–20) | 1 (0–20) |
| Transfusion of plasma (units) | 0 (0–24) | 0 (0–24) |
| Peak post-operative troponin T level (μg/L) | 0.46 (0.07–14.15) | 0.67 (0.17–7.79) |
| Peak post-operative C-reactive protein level (mg/L) | 208 (38–471) | 202 (34–360) |
| Re-operation or major bleeding (%) | 14.3 | 16.3 |
| CVA (%) | 1.2 | 3.5 |
| Length of hospital stay (days) | 8 (5–29) | 8 (6–30) |
| Death (%) | | |
| Early | 2 | 0 |
| Late | 0 | 1 |

Data are presented as median (range) or percentage. PUFA, polyunsaturated fatty acids; RBC, red blood cells; CVA, cerebrovascular accident. No significant difference was found between the groups for any variable, $P > 0.05$, Wilcoxon–Mann–Whitney or Fisher's exact tests.

**Table 4 Adverse effects in the *n*-3 PUFA and placebo groups**

| | *n*-3 PUFA group (*n* = 83) | Placebo group (*n* = 85) |
|---|---|---|
| Adverse effects leading to termination of study treatment | | |
| Gastrointestinal symptoms | 2* | 0 |
| Increased tremor in Parkinson disease | 1 | 0 |
| Adverse effects not leading to termination of study treatment | | |
| Cod liver oil aftertaste | 5* | 1 |
| Gastrointestinal symptoms | 4* | 2 |
| Post-operative infections | 5 | 7 |
| Acute kidney injury | 3 | 2 |
| Pancreatitis, gallstones, jaundice | 2 | 1 |
| Arrhythmias other than POAF | 50 | 47 |
| Heart failure symptoms | 4 | 4 |

Data are presented as absolute numbers. PUFA, polyunsaturated fatty acids. *Combined cod liver oil aftertaste and gastrointestinal symptoms, $P = 0.02$ compared with the placebo group, Fisher's exact test.

more complex surgery, 68.1 vs. 81.8% ($P = 0.04$), than those without POAF. The peak post-operative C-reactive protein levels were higher among the patients with POAF compared with those without POAF, 219 (36–471) vs. 195 (34–370) mg/L, respectively ($P = 0.012$). The hospital stay was longer among patients who developed POAF compared with those who did not, 9 (6–29) days compared with 7 (5–30) days, respectively ($P < 0.001$). Finally, the concentration of total plasma *n*-3 PUFA on the day of surgery was higher in patients with POAF than those without POAF, 111.2 (47.3–256.1) vs. 92.8 (47.5–177.9) μg/mL, respectively ($P = 0.006$).

Multivariable logistic regression analysis showed that advanced age, peak post-operative C-reactive protein level, lower BMI, an operative procedure other than a simple CABG, and non-smoking were associated with a higher risk of developing POAF (*Table 6*). There was no association between POAF and assignment to *n*-3 PUFA treatment, plasma levels of *n*-3 PUFA, use of β-blockers, or other variables tested.

Apart from the patients who received the study medication for <5 days, there were five protocol deviations. One person in the placebo group had a history of AF unknown to the research team, experienced AF in the operating room, and had a concomitant MAZE operation performed. This patient developed POAF. Post-operatively, four patients received short-term treatment with amiodarone for other arrhythmias than AF, of whom three were in the *n*-3 PUFA group and one in the placebo group. None of them developed POAF.

## Discussion

The results of this randomized, double-blinded, placebo-controlled study show no benefit of treatment with *n*-3 PUFA on the incidence of POAF. Moreover, there was no evidence for a beneficial effect of a higher concentration of plasma *n*-3 PUFA on the incidence of POAF.

Although the pathophysiology of POAF likely involves complex interplay of pre-disposing intra-operative and post-operative factors, there is accumulation of data suggesting that inflammation may play an important role.[16] The trauma caused by the surgery initiates an inflammatory response, both locally in the atria and systemically, that is reflected by an increase in C-reactive protein levels.[10,16] However, although ECC alone can cause a systemic inflammatory response, the incidence of POAF is similar in those patients who have undergone surgery with or without cardiopulmonary bypass.[17,18] It is plausible that local inflammation in the atria may alter atrial conduction and create conditions that favour re-entry and arrhythmias. In the light of both the anti-inflammatory effect of *n*-3 PUFA, mediated by lowering the levels of pro-inflammatory eicosanoids derived from arachidonic acid and by decreasing the production of pro-inflammatory cytokines,[19–25] and their potential anti-arrhythmic effect,[12,26–28] it has been speculated that *n*-3 PUFA might be useful in the prevention of POAF.

Consumption of fish products with a high *n*-3 PUFA content has been associated with a decrease in the incidence of AF, not associated with cardiac surgery, over a follow-up period of 12 years.[29] We are aware of only two published studies on the use of *n*-3 PUFA for the prevention of POAF.[13,14] The study carried out by Calo *et al.*[13] in Italy was an open-label, prospective, randomized trial consisting of 160 CABG patients. The incidence of POAF in the *n*-3 PUFA-treated group was 15.2% compared with 33.3% in the control group, portraying *n*-3 PUFA as a promising therapy

**Table 5 Baseline and operative characteristics of patients who did or did not develop post-operative atrial fibrillation**

| | POAF ($n$ = 91) | No POAF ($n$ = 77) |
|---|---|---|
| Age (years) | 69(45–82)* | 65 (43–79) |
| BMI (kg/m$^2$) | 26.7 (17.2–38.1)** | 28.3 (20.9–41.3) |
| Ejection fraction (%) | 60 (15–77.5) | 60 (15–75) |
| Length of treatment (days) | 6 (2–28) | 6 (3–12) |
| Gender (% men) | 79.1 | 79.2 |
| Smoking (%) | 14.3 | 24.7 |
| Cod liver oil intake (%) | 56.0 | 53.2 |
| $n$-3 PUFA intake (%) | 29.4 | 23.4 |
| Use of β-blocker (%) | 71.4 | 81.8 |
| Hypertension (%) | 62.6 | 63.6 |
| Diabetes (%) | 13.3 | 18.2 |
| CABG only (%) | 68.1*** | 81.8 |
| Off-pump surgery (%) | 8.8 | 15.6 |
| ECC time (min) | 102.5 (0–261) | 92 (0–194) |
| Aortic cross-clamp time (min) | 49 (0–208) | 48 (0–142) |
| Estimated operative blood loss (mL) | 1000 (0–6200) | 900 (0—4300) |
| Blood volume in drains (mL) | 800 (175–4980) | 705 (110–3070) |
| Transfusion of RBC (units) | 1 (0–20) | 1 (0–18) |
| Peak post-operative C-reactive protein level (mg/L) | 219 (36–471)** | 195 (34–370) |
| Length of stay (days) | 9 (6–29)**** | 7 (5–30) |
| Re-operation or major bleeding (%) | 15.4 | 15.6 |
| CVA (%) | 2.2 | 2.6 |

Data are presented as median (range) or percentage. POAF, post-operative atrial fibrillation; BMI, body mass index; PUFA, polyunsaturated fatty acids; CABG, coronary artery bypass grafting; ECC extracorporeal circulation RBC, red blood cells; CVA, cerebrovascular accident.
*$P = 0.001$, **$P = 0.012$, ***$P = 0.04$, **** $P < 0.001$, compared with the no-POAF group, Wilcoxon–Mann–Whitney or $\chi^2$ tests.

**Table 6 Multivariable logistic regression analysis[a] of predictors of post-operative atrial fibrillation**

| | $R^2$ | $P$-value | OR (95% CI) |
|---|---|---|---|
| Age | 0.112 | <0.001 | 1.073 (1.033–1.114) |
| Peak post-operative C-reactive protein level (mg/L) | 0.169 | 0.007 | 1.006 (1.002–1.010) |
| BMI | 0.207 | 0.023 | 0.896 (0.815–0.985) |
| Valvular surgery or complex procedure | 0.243 | 0.024 | 2.590 (1.133–5.921) |
| Smoking | 0.269 | 0.049 | 0.405 (0.169–0.994) |

$R^2$, Nagelkerke's $R^2$. Incremental $R^2$ for each step of the regression analysis. BMI, body mass index.
[a]Stepwise forward selection of significant variables.

for the prevention of POAF. The magnitude of the preventive effect of $n$-3 PUFA was in a range similar to that of the effects of amiodarone and β-blockers, including sotalol.[3]

The present study was designed in a manner similar to the Italian study,[13] but in addition the present study was double-blinded and placebo-controlled. Continuous electrocardiographic monitoring was carried out for the duration of hospital stay, whereas the Italian investigators monitored their patients only for the initial 4–5 days after surgery. In addition, patients undergoing valvular heart surgery were included in the present study. Valve replacement surgery and repair have been associated with an increased risk of POAF,[4] which may in part explain the higher incidence of POAF observed in the present study compared with the study by Calo *et al.* (54.2 vs. 24.4%, respectively).

The total daily dose of $n$-3 PUFA was similar (2 g/day) in both the Italian and the present study but differed in the ratio of EPA and DHA. In the Italian study, the $n$-3 PUFA capsules contained EPA and DHA in the ratio of 1:2, whereas in the present study the ratio was 1.2:1. Docosahexaenoic acid may, at lower concentration than EPA, have important inhibitory effects on ion channels, some of which are present only in atrial cells, including $I_{Kur}$.[30,31] A lower dose of DHA in our study could in part explain the observed difference between the studies.

Cod liver oil, which is a rich source of $n$-3 PUFA, is a commonly used dietary supplement in Iceland, particularly among the elderly, and is reflected in relatively high baseline levels of plasma $n$-3 PUFA in the Icelandic population,[32] including the subjects of our study. Plasma $n$-3 PUFA levels were not measured in the study by Calo *et al.*[13] However, a recent, prospective, population-based study of elderly persons (mean age 68.8 ± 15.7 years) in Italy, originally designed by the Laboratory of Clinical Epidemiology of the Italian National Research Council of Aging,[33] showed that the percentage of $n$-3 PUFA in plasma phospholipids was 3.35 ± 0.98% or about one-third of what was observed in the entire cohort of the

present study (9.8 ± 2.80%). A threshold for the incorporation of dietary *n*-3 PUFA into membrane phospholipids has been demonstrated, and that the effects of those fatty acids occur at a relatively low *n*-3 PUFA concentration.[34] This could conceivably explain the beneficial effects of *n*-3 PUFA on incidence of POAF found by Calo *et al.*,[13] whereas this treatment may not be beneficial in a cohort with high baseline *n*-3 PUFA levels such as ours. However, in our study, analysis based on tertiles of *n*-3 PUFA levels at baseline or at operation day did not indicate any trend towards a differential effect of treatment based on *n*-3 PUFA status of the individual.

The administration of oral medications in the first 1–2 days following surgery can sometimes be challenging, which may be important, as this is the time when patients may be at the highest risk of POAF. In the study by Calo *et al.*,[13] *n*-3 PUFA was administered through a nasogastric tube if oral intake was not feasible. Intravenous administration of *n*-3 PUFA peri-operatively also circumvents this problem. Improved bioavailablity may in fact be the reason for the success of this approach as demonstrated by Heidt *et al.*[14]

Even though *n*-3 PUFA treatment was not found to prevent POAF in this study, the results nevertheless support the notion that inflammation may be involved in the pathogenesis of POAF, as the peak post-operative level of C-reactive protein was higher in the patients who developed POAF. Moreover, the peak post-operative C-reactive protein level was, apart from age, the most significant independent predictor of POAF, suggesting a role for inflammation in this setting, which is consistent with previous studies.[10,35] This association seems to be independent of *n*-3 PUFA levels because despite an increase in *n*-3 PUFA plasma levels in the *n*-3 PUFA group, no significant difference was seen in peak C-reactive protein levels between the *n*-3 PUFA and the placebo groups. Although previous studies have also shown that patients undergoing valvular procedures or more complex types of cardiac surgery are more likely to develop POAF, an association with non-smoking and BMI has been less well established and needs to be examined in future studies.[36,37]

Studies evaluating *n*-3 PUFA in the prevention of arrhythmias other than AF in humans, including ventricular tachycardia and ventricular fibrillation, have been somewhat conflicting. Data from experimental and animal studies indicate that *n*-3 PUFA may be effective in preventing severe cardiac arrhythmias and sudden death.[38,39] This is supported by results from the GISSI-Prevenzione trial, where *n*-3 PUFA treatment (1 g/day; EPA and DHA in the ratio of 1:2) was beneficial in decreasing the risk of sudden cardiac death.[40] In contrast, studies in patients with implanted cardiac defibrillator have not shown a beneficial effect on the frequency of ventricular arrhythmias.[41]

Although our study was carefully designed and performed in a double-blinded fashion, it has some limitations, including a relatively low number of participants. However, given the almost identical results in both arms of the study, it is unlikely that a larger study would have yielded different results. It is also worth noting that late arrhythmia occurrences may have been missed, since the patients were not examined following discharge from the hospital. It has been well established that the incidence of POAF peaks in the first 2–4 days after surgery, and this was also the case in the present study, in which the average time from surgery to AF was ~2 days. Thus, it is unlikely that arrhythmia monitoring beyond discharge would have affected the results. Finally, short-term *n*-3 PUFA treatment may be insufficient for the incorporation of *n*-3 PUFA into cell membranes.[42] However, the high baseline levels of *n*-3 PUFA in plasma phospholipids in our subjects may indicate abundance of these fatty acids in their cell membranes. Furthermore, the success of peri-operative intravenous infusion of fish oil for preventing POAF[14] suggests that membrane composition may not be of importance. The relative significance of plasma or cell membrane fatty acid composition needs further investigation.

# Conclusion

The results of this study contradict previous findings and suggest that the use of *n*-3 PUFA supplements 5–7 days prior to open heart surgery and in the immediate post-operative period does not reduce the incidence of POAF among subjects with relatively high baseline *n*-3 PUFA levels.

# Authors' contribution

All authors contributed to the design of the study. R.H., G.V.S., D.O.A., and O.S.I. collected and analysed the data. R.H., G.V.S., D.O.A., O.S.I., and R.P. wrote the initial draft of the manuscript. All authors contributed to the final form of the manuscript.

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